HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.

KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.3)	01/2015
Warnings and Precautions (5.4, 5.6, 5.7)	06/2015

----------INDICATIONS AND USAGE----------

KEYTRUDA is a human programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks. (2.1)
- Dilute prior to intravenous infusion. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

- For injection: 50 mg lyophilized powder in single-use vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial (3)

----------CONTRAINDICATIONS----------

None. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Immune-mediated adverse reactions: Administer corticosteroids based on the severity of the reaction. (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)
  - Immune-mediated pneumonitis: Withhold for moderate, and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
  - Immune-mediated colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
  - Immune-mediated hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
  - Immune-mediated endocrinopathies:
    - Hypophysitis: Withhold for moderate, withhold or discontinue for severe, and permanently discontinue for life-threatening hypophysitis. (5.4)
    - Thyroid disorders: Monitor for changes in thyroid function. Withhold for severe and permanently discontinue for life-threatening hyperthyroidism. (5.4)
    - Type 1 diabetes mellitus: Monitor for hyperglycemia. Administer insulin for type 1 diabetes and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved. (5.4)
  - Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.7)
- Embryofetal toxicity: KEYTRUDA may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.8)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (reported in ≥20% of patients) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Nursing mothers: Discontinue nursing or discontinue KEYTRUDA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor *[see Clinical Studies (14)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.2 Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Symptomatic hypophysitis *[see Warnings and Precautions (5.4)]*
- Grade 2 nephritis *[see Warnings and Precautions (5.5)]*
- Grade 3 hyperthyroidism *[see Warnings and Precautions (5.4)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.6)]*

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.7)]*
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.6)]*

2.3 Preparation and Administration

Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Reconstituted and Diluted Solutions

The product does not contain a preservative.

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Administration

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg lyophilized powder in a single-use vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

Pneumonitis occurred in 12 (2.9%) of 411 melanoma patients, including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to development of pneumonitis was 5 months (range 0.3 weeks to 9.9 months). The median duration was 4.9 months (range 1 week to 14.4 months). Five of eight patients with Grade 2 and the one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. The median initial dose of high-dose corticosteroid treatment was 63.4 mg/day of prednisone or equivalent with a median duration of treatment of 3 days (range 1 to 34) followed by a corticosteroid taper. Pneumonitis led to discontinuation of KEYTRUDA in 3 (0.7%) patients. Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis.

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) pneumonitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.2 Immune-Mediated Colitis

Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to onset of colitis was 6.5 months (range 2.3 to 9.8). The median duration was 2.6 months (range 0.6 weeks to 3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4 to 41), followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of KEYTRUDA due to colitis. All four patients with colitis experienced complete resolution of the event.

Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.3 Immune-Mediated Hepatitis

Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving KEYTRUDA in Trial 1. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued KEYTRUDA and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

Hypophysitis occurred in 2 (0.5%) of 411 patients, consisting of one Grade 2 and one Grade 4 case (0.2% each), in patients receiving KEYTRUDA in Trial 1. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose.

Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis, withhold or discontinue KEYTRUDA for severe (Grade 3) hypophysitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

Thyroid Disorders

Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to onset was 1.5 months (range 0.5 to 2.1). The median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of KEYTRUDA due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event.

Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving KEYTRUDA in Trial 1. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks to 19 months). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued KEYTRUDA for management of hypothyroidism.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Administer corticosteroids for Grade 3 or greater hyperthyroidism, withhold KEYTRUDA for severe (Grade 3) hyperthyroidism, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

Type 1 Diabetes mellitus

Type 1 diabetes mellitus, including diabetic ketoacidosis, has occurred in patients receiving KEYTRUDA. Monitor patients for hyperglycemia and other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.5 Renal Failure and Immune-Mediated Nephritis

Nephritis occurred in 3 (0.7%) patients, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. The time to onset of autoimmune nephritis was 11.6 months after the first dose of KEYTRUDA (5 months after the last dose) and lasted 3.2 months; this patient did not have a biopsy. Acute interstitial nephritis was confirmed by renal biopsy in two patients with Grades 3-4 renal failure. All three patients fully recovered renal function with treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.

Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2) nephritis, and permanently discontinue KEYTRUDA for severe (Grade 3), or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.6 Other Immune-Mediated Adverse Reactions

Other clinically important immune-mediated adverse reactions can occur.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with KEYTRUDA in Trial 1: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma.

Across clinical studies with KEYTRUDA, the following clinically significant, immune-mediated adverse reactions have occurred: severe dermatitis including bullous pemphigoid, myasthenic syndrome, optic neuritis, and rhabdomyolysis.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less. Permanently discontinue KEYTRUDA for any severe or Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.7 Infusion-Related Reactions

Infusion-related reactions, including severe and life-threatening reactions, have occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritis, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.2)]*.

5.8 Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA *[see Use in Specific Populations (8.1, 8.8)].*

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)].*
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.3)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)]*.
- Renal failure and immune-mediated nephritis *[see Warnings and Precautions (5.5)]*.
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.6)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.7)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS and PRECAUTIONS section reflect exposure to KEYTRUDA in Trial 1, an uncontrolled, open-label, multiple cohort trial in which 411 patients with unresectable or metastatic melanoma received KEYTRUDA at either 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks. The median duration of exposure to KEYTRUDA was 6.2 months (range 1 day to 24.6 months) with a median of 10 doses (range 1 to 51). The study population characteristics were: median age of 61 years (range 18 to 94), 39% age 65 years or older, 60% male, 97% white, 73% with M1c disease, 8% with brain metastases, 35% with elevated LDH, 54% with prior exposure to ipilimumab, and 47% with two or more prior systemic therapies for advanced or metastatic disease.

KEYTRUDA was discontinued for adverse reactions in 9% of the 411 patients. Adverse reactions, reported in at least two patients, that led to discontinuation of KEYTRUDA were: pneumonitis, renal failure, and pain. Serious adverse reactions occurred in 36% of patients receiving KEYTRUDA. The most frequent serious adverse drug reactions reported in 2% or more of patients in Trial 1 were renal failure, dyspnea, pneumonia, and cellulitis.

Table 1 presents adverse reactions identified from analyses of the 89 patients with unresectable or metastatic melanoma who received KEYTRUDA 2 mg/kg every three weeks in one cohort of Trial 1. Patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This cohort of Trial 1 excluded patients with severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV or hepatitis B or C. Of the 89 patients in this cohort, the median age was 59 years (range 18 to 88), 33% were age 65 years or older, 53% were male, 98% were white, 44% had an elevated LDH, 84% had Stage M1c disease, 8% had brain metastases, and 70% received two or more prior therapies for advanced or metastatic disease. The median duration of exposure to KEYTRUDA was 6.2 months (range 1 day to 15.3 months) with a median of nine doses (range 1 to 23). Fifty-one percent of patients were exposed to KEYTRUDA for greater than 6 months and 21% for greater than 1 year.

KEYTRUDA was discontinued for adverse reactions in 6% of the 89 patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

Table 1: Adverse Reactions in ≥10% of Patients with Unresectable or Metastatic Melanoma

	KEYTRUDA 2 mg/kg every 3 weeks N=89	
Adverse Reaction	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue	47	7
Peripheral Edema	17	1
Chills	14	0
Pyrexia	11	0
Gastrointestinal Disorders		
Nausea	30	0
Constipation	21	0
Diarrhea	20	0
Vomiting	16	0
Abdominal pain	12	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	30	1
Dyspnea	18	2
Skin and Subcutaneous Tissue Disorders		
Pruritus	30	0
Rash	29	0
Vitiligo	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	20	0
Pain in extremity	18	1
Myalgia	14	1
Back pain	12	1
Nervous System Disorders		
Headache	16	0
Dizziness	11	0
Blood and Lymphatic System Disorders		
Anemia	14	5
Psychiatric Disorders		
Insomnia	14	0
Infections and Infestations		
Upper respiratory tract infection	11	1

* There were no Grade 5 adverse reactions reported. Of the ≥10% adverse reactions, none was reported as Grade 4.

Other clinically important adverse reactions observed in up to 10% of patients treated with KEYTRUDA were:

Infections and infestations: sepsis

Table 2: Laboratory Abnormalities Increased from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma

	KEYTRUDA 2 mg/kg every 3 weeks N=89	
Laboratory Test	**All Grades %**	**Grades 3-4 %**
Chemistry		
Hyperglycemia	40	2*
Hyponatremia	35	9
Hypoalbuminemia	34	0
Hypertriglyceridemia	25	0
Increased Aspartate Aminotransferase	24	2*
Hypocalcemia	24	1
Hematology		
Anemia	55	8*

* Grade 4 abnormalities in this table limited to hyperglycemia, increased aspartate aminotransferase, and anemia (one patient each)

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Because trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In this analysis, none of the 97 patients who were treated with 2 mg/kg every 3 weeks tested positive for treatment-emergent anti-pembrolizumab antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D.

Risk Summary

Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice.

Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Based on its mechanism of action,

fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

8.3 Nursing Mothers
It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA.

8.4 Pediatric Use
Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

8.5 Geriatric Use
Of the 411 patients treated with KEYTRUDA, 39% were 65 years and over. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

8.6 Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with renal impairment *[see Clinical Pharmacology (12.3)].*

8.7 Hepatic Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with mild hepatic impairment [total bilirubin (TB) less than or equal to ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST]. KEYTRUDA has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)].*

8.8 Females and Males of Reproductive Potential
Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].* Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for at least 4 months following the last dose of pembrolizumab.

10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

11 DESCRIPTION

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling

through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life ($t_{1/2}$) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 18 to 94 years), gender, renal impairment, mild hepatic impairment, and tumor burden. The effect of race could not be assessed due to limited data available in non-White patients.

Renal Impairment: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=210), moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=43), or severe (eGFR 15 to 29 mL/min/1.73 m^2; n=2) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function *[see Use in Specific Populations (8.6)].*

Hepatic Impairment: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see Use in Specific Populations (8.7)].*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of

pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

The efficacy of KEYTRUDA was investigated in a multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating cohort of Trial 1. Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; and a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks. Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of KEYTRUDA every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 12 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review and duration of response.

Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The ORR was 24% (95% confidence interval: 15, 34) in the 2 mg/kg arm, consisting of 1 complete response and 20 partial responses. Among the 21 patients with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.2 months after initial response. The remaining 18 patients (86%) had ongoing responses with durations ranging from 1.4+ to 8.5+ months, which included 8 patients with ongoing responses of 6 months or longer. One additional patient developed two new asymptomatic lesions at the first tumor assessment concurrent with a 75% decrease in overall tumor burden; KEYTRUDA was continued and this reduction in tumor burden was durable for 5+ months.

There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. Similar ORR results were observed in the 10 mg/kg arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (lyophilized powder): carton containing one 50 mg single-use vial (NDC 0006-3029-02).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
- Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)].*
- Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)].*
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.
- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.
- Advise women that KEYTRUDA may cause fetal harm. Instruct women of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.8)]*.
- Advise nursing mothers not to breastfeed while taking KEYTRUDA *[see Use in Specific Populations (8.3)]*.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
U.S. License No. 0002

For KEYTRUDA for injection, at:
Schering-Plough (Brinny) Co.,
County Cork, Ireland

For KEYTRUDA injection, at:
MSD Ireland (Carlow)
County Carlow, Ireland

For patent information: www.merck.com/product/patent/home.html

uspi-mk3475-iv-1506r002

MEDICATION GUIDE

KEYTRUDA® (key-true-duh) (pembrolizumab) for injection	**KEYTRUDA® (key-true-duh) (pembrolizumab) injection**

What is the most important information I should know about KEYTRUDA?

KEYTRUDA is a medicine that may treat your melanoma by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening.

Call or see your doctor right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Symptoms of pneumonitis may include:
- shortness of breath
- chest pain
- new or worse cough

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:
- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:
- yellowing of your skin or the whites of your eyes
- nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine
- feeling less hungry than usual
- bleeding or bruising more easily than normal

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:
- rapid heart beat
- weight loss or weight gain
- increased sweating
- feeling more hungry or thirsty
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- muscle aches
- dizziness or fainting
- headaches that will not go away or unusual headache

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:
- change in the amount or color of your urine.

Problems in other organs. Signs of these problems may include:
- rash
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness

Infusion (IV) reactions, that can sometimes be severe and life-threatening. Signs and symptoms of

infusion reactions may include:

- chills or shaking
- shortness of breath or wheezing
- itching or rash
- flushing
- dizziness
- fever
- feeling like passing out

Getting medical treatment right away may help keep these problems from becoming more serious. Your doctor will check you for these problems during treatment with KEYTRUDA. Your doctor may treat you with corticosteroid medicines and delay or completely stop treatment with KEYTRUDA, if you have severe side effects.

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat a kind of skin cancer called melanoma. KEYTRUDA may be used when your melanoma:

- has spread or cannot be removed by surgery (advanced melanoma)
  and,
- after you have tried a medicine call ipilimumab and it did not work or is no longer working
  and,
- if your tumor has an abnormal "BRAF" gene, and you also have tried a different medicine called a BRAF inhibitor, and it did not work or is no longer working.

It is not known if KEYTRUDA is safe and effective in children less than 18 years of age.

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant
  - KEYTRUDA may harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 4 months after the last dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you become pregnant during treatment with KEYTRUDA.
- Are breastfeeding or plan to breastfeed.
  - It is not known if KEYTRUDA passes into your breast milk.
  - Do not breastfeed during treatment with KEYTRUDA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive KEYTRUDA?

- Your doctor will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- KEYTRUDA is usually given every 3 weeks.
- Your doctor will decide how many treatments you need.
- Your doctor will do blood tests to check you for side effects.
- If you miss any appointments, call your doctor as soon as possible to reschedule your appointment.